What is claimed:

1. A method of identifying binding sites on a macromolecule comprising:

(a) for at least one organic fragment (ORF), conducting, at separate values of parameter *B*, two or more simulated annealing of chemical potential calculations using the ORF as the inserted solvent; and

(b) comparing converged solutions from step (a) to identify first locations at which the relevant ORF is strongly bound, thereby identifying candidate sites for binding ligand molecules.

2. The method of claim 1, further comprising:

(c) identifying clusters of sites that strongly bind an ORF.

3. The method of claim 2, further comprising:

(d) conducting steps (a) and (b) for each of two or more ORFs and identifying clusters where two or more distinct ORFs bind.

4. The method of claim 3, wherein a cluster that binds three or more distinct ORFs is identified.

5. The method of claim 3, further comprising reducing the binding stringency in the vicinity of a cluster to further identify elements that would contribute to the binding of a bioactive agent.

6. The method of ~~claim 1~~ claim 3, further comprising:

(e) conducting, at separate values of a measure of chemical potential, two or more simulated annealing of chemical potential calculations using water as the inserted solvent;

(f) comparing converged solutions from step (c) to identify locations at which water is strongly bound, thereby identifying water locations which are not candidate sites for binding ligand molecules; and

(g) identifying first locations that are not water locations.

7. The method of claim 1,wherein the simulated annealing of chemical potential calculations comprise multiple steps of sampling, and wherein in a number of steps of the sampling the ORFs position is changed by a small amount and the resulting new position is accepted or rejected based on the change in energy as a result of the change attempted.

8. A method of identifying the chemical characteristics of compounds that bind a macromolecule comprising examining the functionalities and relative orientations of the ORFs found in a cluster pursuant to the binding site identifying method of claim 3.

9. A method of conducting combinatorial chemistry to identify compounds that interact with a macromolecule comprising:

(a) identifying classes of reactants that are modeled by the functionalities of the ORFs found in a cluster pursuant to the binding site identifying method of claim 3;

(b) designing a combinatorial synthetic protocol that calls for two or more synthetic procedures that react reagents of at least two of the classes identified in step (a); and

(c) conducting the combinatorial synthetic protocol to create candidate binding molecules.

10. A method of conducting a bioactive agent discovery process comprising:

(a) from a group of established combinatorial synthetic protocols or collections of chemical compounds or pools of chemical compounds, identifying those members of the group that provide a high density of compounds that meet for a macromolecule selection criteria identified from the binding site identifying method of claim 3; and

(b) conducting binding or functional assays to identify compounds obtained from the identified collections or protocols which bind or affect the function of the macromolecule.